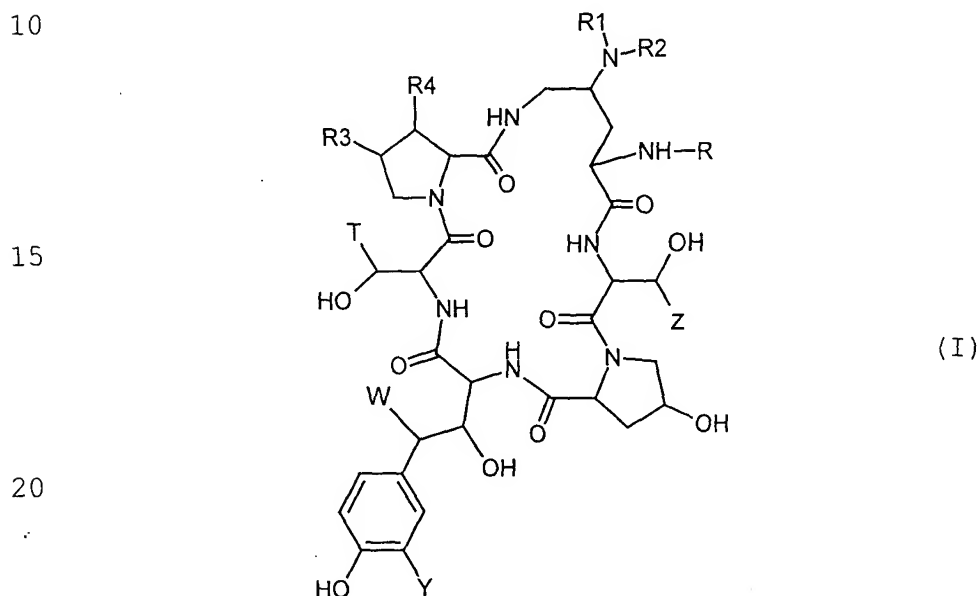


New derivatives of echinocandine, their preparation process  
and their use as antifungals.

-- This is a 371 of PCT/FR00/01568 filed June 8, 2000.--

The present invention relates to new derivatives of  
 5 echinocandine, their preparation process and their use as  
 antifungals.

A subject of the invention is, in all possible isomer  
 forms as well as their mixtures, the compounds of formula  
 (I):

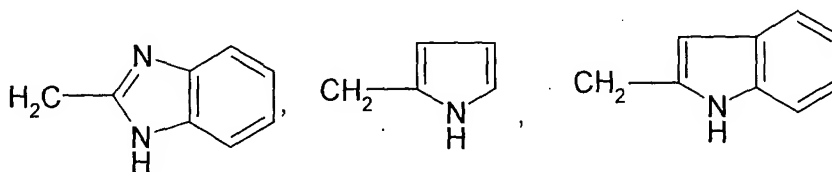


in which

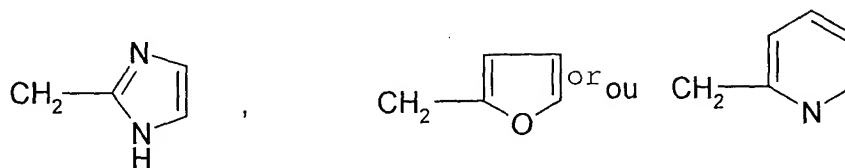
25 either  $R_1$  represents a hydrogen atom or a methyl radical.

$R_2$  represents a cyclohexyl radical substituted by an amine, a  
 $\text{CH}_2\text{CH}_2\text{NHCH}_3$  radical, a  $\text{CH}_2\text{CHCH}_3\text{NH}_2$  radical, a

30



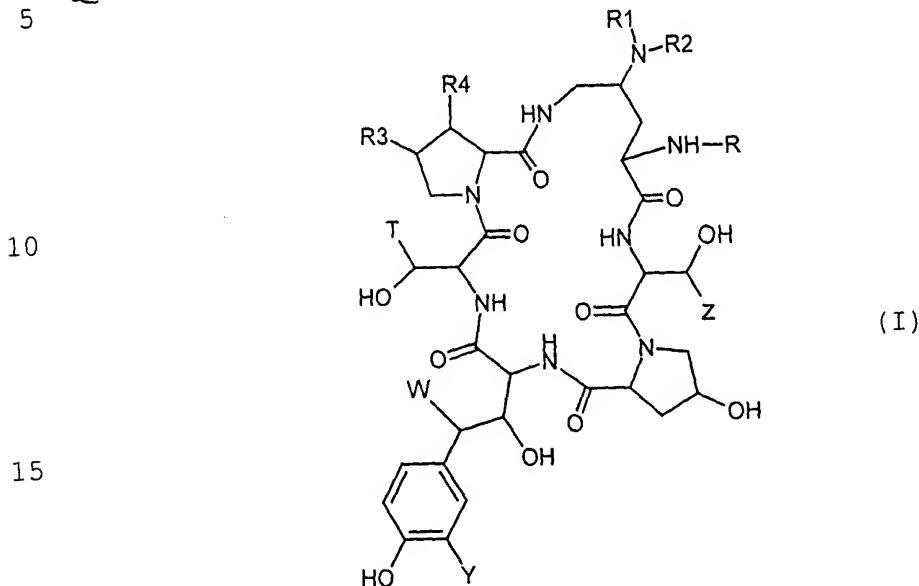
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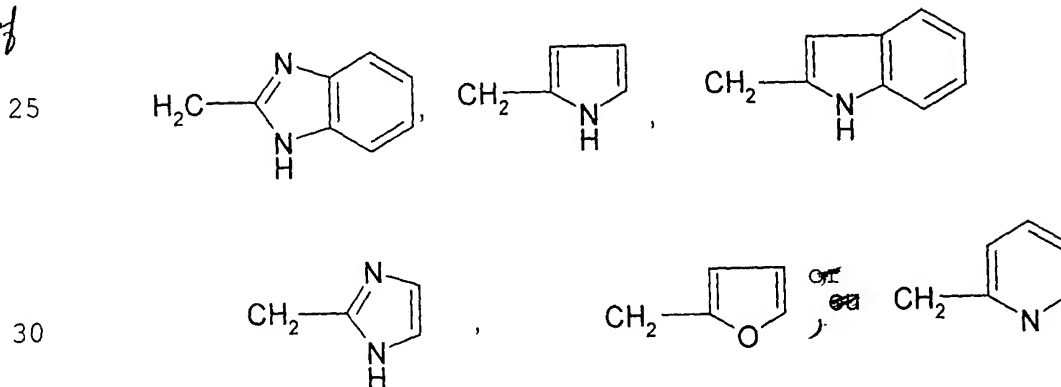
radical, a  $\text{CHCH}_3\text{CH}_2\text{NH}_2$  radical, a  $-(\text{CH}_2)_a\text{OH}$  radical, a

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- 1) ~~all possible isomeric forms as well as their mixtures,~~ <sup>and</sup>  
the compounds of ~~the~~ <sup>the</sup> formula (I).



- in which
- 20 either  $R_1$  ~~represents a hydrogen atom or a methyl radical,~~ <sup>is</sup> ~~and~~  
 $R_2$  ~~represents a cyclohexyl radical substituted by an amine,~~ <sup>is</sup>  
 $\text{CH}_2\text{CH}_2\text{NHCH}_3$  ~~radical,~~ <sup>is</sup>  $\text{CH}_2\text{CHCH}_3\text{NH}_2$  ~~radical,~~ <sup>is</sup>



- 35 ~~representing an integer comprised between 1 and 8,~~ <sup>where</sup>  $(\text{CH}_2)_b$ -  
 $\text{C}\equiv\text{N}$  ~~radical~~ <sup>is</sup>  
 $b$  ~~representing an integer comprised between 1 and 8,~~ <sup>is</sup> ~~and~~  
 $\text{CHCH}_3\text{C}_6\text{H}_5$  ~~radical,~~ <sup>is</sup>  $(\text{CH}_2)-\text{C}(\text{CH}_3)_2\text{NHCOCF}_3$  ~~radical,~~ <sup>is</sup> ~~and~~

CHCH<sub>3</sub>(CH<sub>2</sub>)<sup>d</sup> radical, <sup>where</sup> d <sup>is</sup> representing an integer <sup>of</sup> comprised between 1 <sup>to</sup> and 8

or R<sub>1</sub> and R<sub>2</sub> together with the nitrogen <sup>to which they are attached</sup> which carries them form a ring <sup>of</sup> 3, 4 or 5 carbons optionally substituted by

5 an amine

R<sub>3</sub> <sup>is</sup> represents a hydrogen atom, a methyl <sup>and</sup> or hydroxyl radical

R<sub>4</sub> <sup>is</sup> represents a hydrogen atom or a hydroxyl radical

R <sup>is</sup> represents a linear or branched <sup>alkyl and</sup> or cyclic <sup>alkyl or</sup> chain containing up to 30 carbon atoms, optionally containing <sup>at least</sup> one or more

10 heteroatoms, <sup>at least</sup> one or more heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms optionally containing <sup>at least</sup> one or more heteroatoms and/or <sup>at least</sup> one or more heterocycles,

T <sup>is</sup> represents a hydrogen atom, a methyl radical, a -CH<sub>2</sub>CONH<sub>2</sub>, 15 -CH<sub>2</sub>C≡N radical, a -(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub> <sup>and</sup> or -(CH<sub>2</sub>)<sub>2</sub>Nalk<sup>+</sup>X<sup>-</sup> radical, X <sup>is</sup> being a halogen atom and alk <sup>is</sup> an alkyl radical containing up to 8 carbon atoms,

Y <sup>is</sup> represents a hydrogen atom, a hydroxyl, radical or a halogen atom <sup>and</sup> or an -OSO<sub>3</sub>H radical or one of the salts <sup>thereof</sup> of this radical,

20 W <sup>is</sup> represents a hydrogen atom or an -OH radical,

Z <sup>is</sup> represents a hydrogen atom or a methyl radical, <sup>and its non-toxic,</sup>

<sup>pharmaceutically acceptable and</sup> as well as the addition salts with acids of the products of formula (I).

2) <sup>A</sup> The compounds of formula (I) defined in claim 1 in which

25 T <sup>is</sup> represents a hydrogen atom.

3) <sup>A</sup> The compounds of formula (I) defined in claim 1 or 2 in which W <sup>is</sup> represents a hydrogen atom.

4) <sup>A</sup> The compounds of formula (I) defined in any one of claims 1 to 3, in which Z <sup>is</sup> represents a methyl radical.

30 5) <sup>A</sup> The compounds of formula (I) defined in any one of claims 1 to 4 in which Y <sup>is</sup> represents a hydrogen atom.

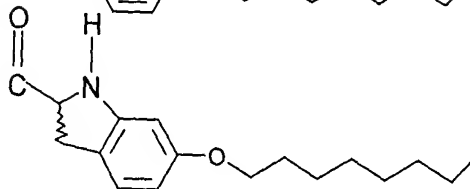
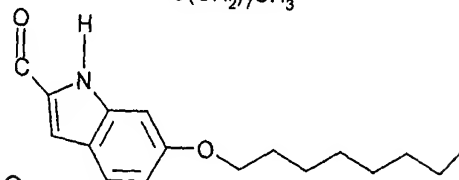
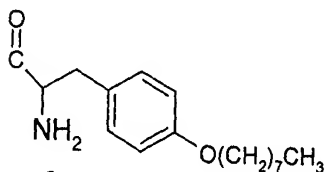
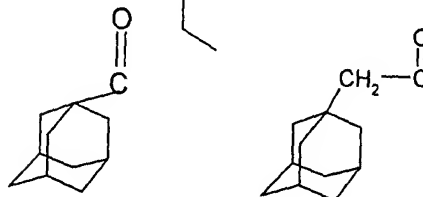
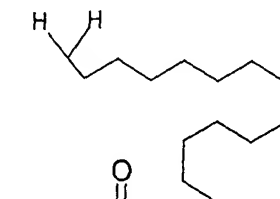
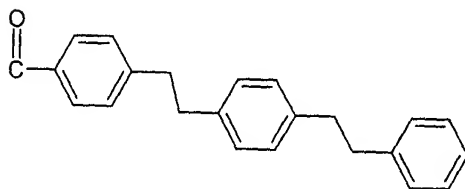
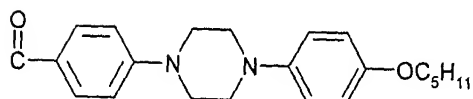
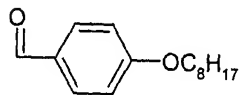
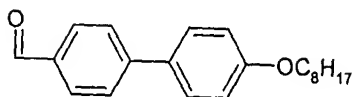
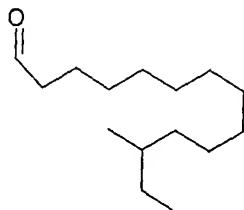
6) <sup>A</sup> The compounds of formula (I) defined in any one of claims 1 to 5 in which R<sub>3</sub> <sup>is</sup> represents a methyl radical.

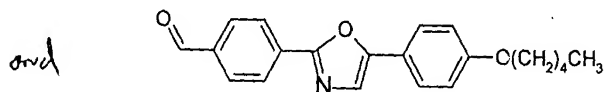
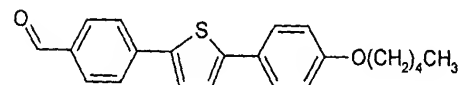
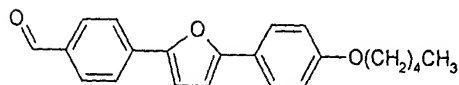
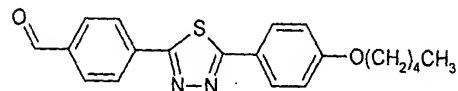
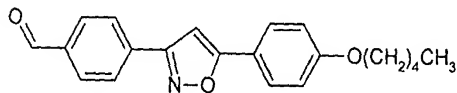
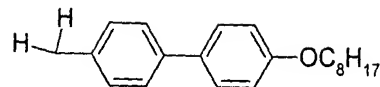
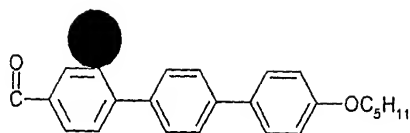
7) <sup>A</sup> The compounds of formula defined in any one of claims 1 to 6 in which R<sub>4</sub> <sup>is</sup> represents a hydroxyl radical.

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8) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 7 in which R ~~is selected from~~ *the group consisting of*

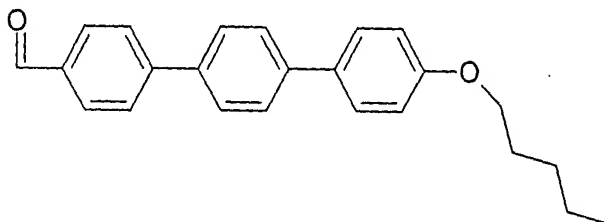
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radical.

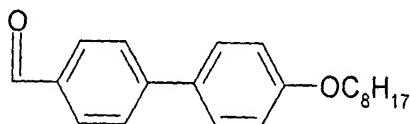
- 9) <sup>A</sup> The compound of formula (I) defined in claim 8, in which R <sup>is</sup> represents a



10

chain.

- 10) <sup>A</sup> The compound of formula (I) defined in claim 8, in which R <sup>is</sup> represents a

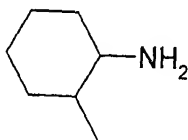


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chain.

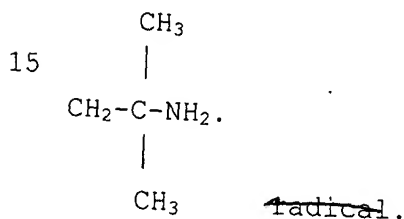
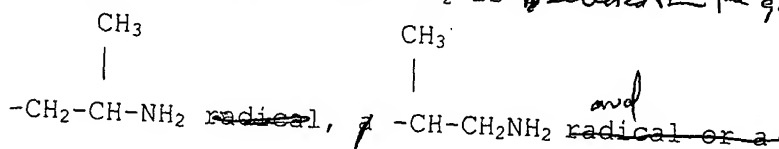
- 11) <sup>A</sup> The compound of formula (I) defined in any one of claims 1 to 10 in which R<sub>1</sub> is a <sup>hydrogen</sup> hydrogen atom.

- 12) <sup>A</sup> ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is~~

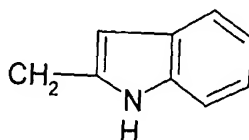
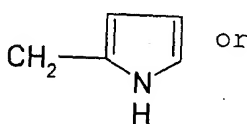


5 ~~radical.~~

- 13) <sup>A</sup> ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is~~ *selected from the group consisting of*



- 20 14) <sup>A</sup> ~~The compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is~~

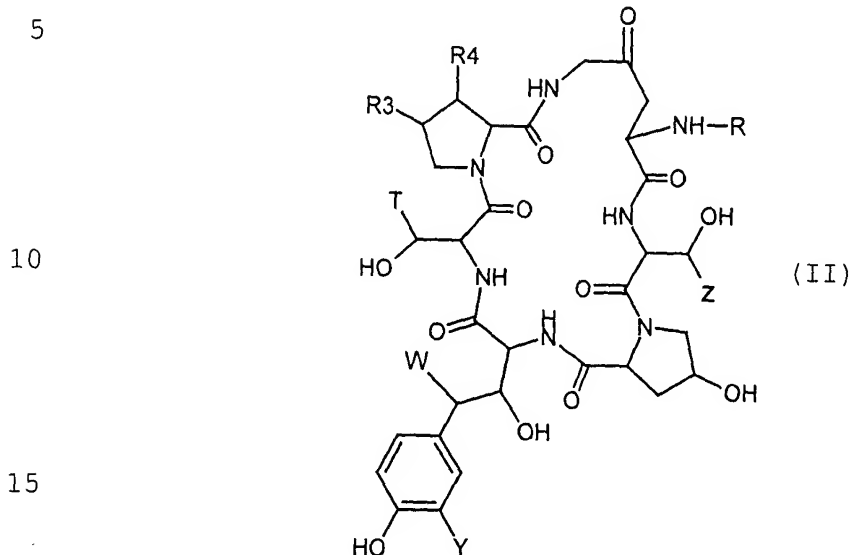


~~radical.~~

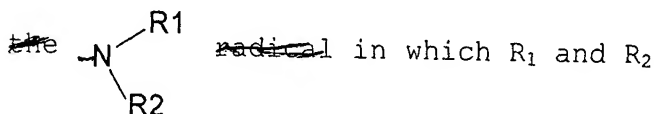
- 15) <sup>A</sup> ~~The compounds of formula (I) defined in any one of~~  
 30 ~~claims 1 to 14 the names of which follow:~~ *selected from the group consisting of*  
 - 1-[4-[[[(1H-benzimidazol-2-yl)-methyl]-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-  
 echinocandine B trifluoroacetate (isomer B), *and*  
 35 - trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-  
 echinocandine B trifluoroacetate (isomer A).

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16) ~~A process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15 characterized in that a compound of formula (II)~~ <sup>a</sup> ~~comprising reacting a~~



wherein ~~in which~~ <sup>are defined as in claim 1</sup> ~~retain their previous~~ <sup>with</sup> ~~meaning, is subjected to the action of~~ an amine or amine derivative capable of introducing



25 ~~are defined as in claim 1~~ <sup>optionally</sup> ~~retain their previous meaning and is desired~~ to the action of a reducing agent and/or an amine functionalization agent, and/or an acid ~~in order~~ to form the salt of the product of claim 1 obtained,

30 and/or a separation agent of the different isomers obtained, and the sought compound of formula (I) is thus obtained.

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

35 18) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.


--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,  
BIERMAN, MUSERLIAN AND LUCAS

  
Charles A. Muserlian, #19,683  
Attorney for Applicant(s)  
Tel. # (212) 661-8000

CAM:sd

Enclosures: Marked-Up Version of Specification and Claims  
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